

Toxicity and side-effects of antimalarials in Africa: a critical review

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Notwithstanding the presence of resistance to chloroquine in some parts of Africa, this drug is still the most widely used antimalarial in the continent. One adverse reaction of chloroquine that has an important bearing on its use is pruritus. The risk of increasing the incidence of ocular toxicity through prolonged use of chloroquine for prophylaxis must be borne in mind by physicians. Another antimalarial that is likely to be used in increasing amounts in Africa is pyrimethamine–sulfadoxine. With prolonged use of this combination for prophylaxis, the adverse reactions usually associated with the long-acting sulfonamides are possible.

Genetic abnormalities may also play a part in the incidence and severity of adverse reactions to certain drugs, e.g., primaquine and quinine. Most of the common adverse reactions are mild and have little or no influence on the acceptability and utilization of the drugs, with the exception of chloroquine-induced pruritus. Studies to define the precise epidemiology and pathophysiology of this reaction are urgently needed.

The antimalarials in current use in Africa can be classified as follows:

- (1) the 4-aminoquinolines, e.g., chloroquine, hydroxychloroquine, and amodiaquine;
- (2) the 8-aminoquinolines, e.g., primaquine;
- (3) quinine;
- (4) the dihydrofolate reductase inhibitors, e.g., proguanil and pyrimethamine;
- (5) a dihydrofolate reductase inhibitor plus a sulfonamide or sulfone, e.g., Fansidar (sulfadoxine plus pyrimethamine) and Maloprim (dapsone plus pyrimethamine).

The most widely used antimalarials in Africa at present are the 4-aminoquinolines, particularly chloroquine. The toxicity and side-effects of this group of drugs will be described in some detail. The more important reactions to the other drugs will then be highlighted.

CHLOROQUINE AND OTHER 4-AMINOQUINOLINES

Oral administration of a single dose of chloroquine and related drugs may be followed by abdominal discomfort, nausea, vomiting, headache, dizziness, blurring of vision, mental and physical weakness, and fatigue. These symptoms are usually mild and

transient. More severe adverse reactions to the 4-aminoquinolines including itching, cardiovascular abnormalities, dyskinesia, ocular damage, neuromuscular disorders, and hearing loss.

Itching

A mild degree of itching with or without a rash can follow the use of chloroquine in all races. However, in Africans, a more severe itching reaction occurs (1, 2). The itching has a curious biting or pricking character and affects all parts of the body including the scalp, the palms of the hands, and the soles of the feet. It is often unassociated with urticaria or any other kind of rash. It is similar to that experienced by some individuals after bathing—the so-called aquagenic or hydrogenic pruritus (3). It begins within a few hours of taking the drug and often continues for between 48 and 72 hours. It is usually severe enough to make sleep impossible for as long as it lasts. The itching occurs in all age groups but it is unusual for it to be experienced on the first exposure to the drug. Once itching has started, it usually runs its course of 48–72 hours, irrespective of treatment with antihistamines. However, prophylactic administration of an antihistamine usually prevents or reduces the severity of the reaction. It occurs more often in individuals who use chloroquine relatively frequently for the treatment of malaria (three or more times a year). After a long period of not taking the drug, the next use by a reactor is not usually followed by

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this reaction but if he then uses it with increasing frequency, the reaction reappears.

The pathogenesis of the itching is still a matter of debate. The fact that the reaction occurs after two or more courses of the drug suggests a hypersensitivity reaction, but the subsequent course is not typical of such reactions. Olatunde (4) investigated the problem by studying chloroquine concentrations in the plasma and skin of patients prone to itching and those who were not. He found that, after a single dose of chloroquine, plasma chloroquine concentrations were similar in both groups; in the skin, however, patients prone to itching had higher unchanged chloroquine and lower chloroquine metabolites than patients who were not disposed to itching. In recent years chloroquine has been used with increasing frequency in the prophylaxis of malaria by indigenous Africans. Until now, there has been no report of itching in persons using chloroquine prophylactically, even though it occurs in 10–15% of those using it therapeutically (5). This observation raises the possibility that the side-effect may result from some as yet unidentified product of a reaction between chloroquine and the malaria parasites.

Cardiovascular abnormalities

Cardiovascular effects of chloroquine are most commonly observed after parenteral administration of the drug or in toxic overdosage. They may take the forms of hypotension and cardiac arrhythmias and may progress to sudden cardiac arrest and death (6–9). In a recent study, Walker et al. (10) found that approximately 50% of children who reported to a hospital in Nigeria with a pyrexial illness had substantial plasma levels of chloroquine before hospital treatment started. This indicated self-medication with the drug prior to reporting to hospital. They concluded that administration of parenteral chloroquine to such children, even at the recommended dosage, could produce blood levels of the drug that are toxic to the heart. Recent pharmacokinetic studies have shown that chloroquine is rapidly and almost completely absorbed after oral administration in both healthy adult volunteers and malarial children (11, 12). The need for parenteral administration of chloroquine should not arise, therefore, except where oral administration is not feasible, as in subjects in coma or those with repeated vomiting. In such cases, intramuscular would be preferable to intravenous injection. In a recent study on healthy volunteers given intravenous chloroquine, Gustafsson et al. (11) monitored the electrocardiogram and blood pressure and found these to be normal with a dose of 5–10 mg/kg body weight, given slowly. They concluded that intravenous chloroquine could be safe if the drug is given well diluted in a drip over at least 15 minutes.

Although most cases of cardiovascular abnormalities have followed the parenteral administration of chloroquine, cases of heart block were recently reported in two patients on chronic treatment with the drug (13). The cardiovascular effects of chloroquine are probably related to its chemical similarity to quinidine. Thus, under experimental conditions it depresses myocardial contractility, depresses excitability and conductivity of cardiac muscle, and produces peripheral vasodilatation (14).

Dyskinesia

Abnormal involuntary movements similar to those that occur in Parkinsonism have been reported in some patients treated with the 4-aminoquinolines, particularly chloroquine and amodiaquine (15–19). The movements mainly affected the tongue and the facial muscles. In some patients, the limbs were affected as well, leading to tremor and ataxia. The symptoms usually started within 24 hours of taking the drug. If left untreated, the disturbance remitted spontaneously within 48 hours, but it could be terminated within two hours by giving anticholinergic drugs like benzhexol or benztropine. Some of the reported cases had had similar episodes after previous administration of the drug; once they had recovered, the attack could be precipitated again on rechallenge with the drug. Both sexes were affected, but the subjects were usually young people below the age of 30.

Majumdar (20) suggested a mechanism for chloroquine-induced involuntary movements. Chloroquine and the phenothiazines are known to bind avidly to melanin-containing tissues. Melanin is derived from dopa (3-hydroxytyrosine), the biosynthetic pathway being phenylalanine — tyrosine — dopa quinone — melanin. In view of the structural relationship between dopa and melanin, it was inferred that chloroquine would also bind avidly to tissues rich in dopaminergic receptors. When this occurs in dopaminergic receptors in the nigrostriatal system, dopaminergic transmission in this system may be blocked, leading to Parkinsonism-like involuntary movements. Osifo (21) tested this hypothesis by studying the concentration and distribution of chloroquine in different tissues of the brain and found no difference between catecholamine-rich and catecholamine-poor tissues. He therefore proposed an alternative mechanism for the chloroquine-induced dyskinesia. His hypothesis, which has yet to be submitted to experimental test, is based on the weak but specific adrenergic-neurone-blocking action of chloroquine.

Ocular toxicity

The eye changes that occur with chloroquine usually follow prolonged administration of the drug, especially when it is used in the treatment of rheuma-

toid arthritis. The eye changes may occur in the retina, cornea, lens, or optic nerve. The retinopathy is characterized by macular and perimacular degeneration, patchy depigmentation of the macula, and retinal artery constriction. A "bull's-eye" appearance may result from an oval perifoveal distribution of the lesions. The corneal lesions may range from diffuse punctate deposits below the epithelium to dense, less regular, yellow pigmented lines beneath the centre of the cornea. These changes result in loss of central visual acuity, which may progress to total blindness.

Although ocular toxicity of chloroquine was associated in the past only with its long-term use in non-malarial diseases, recent reports show that it may also occur with the prolonged use of chloroquine in the prophylaxis of malaria (22). Furthermore, the complication may be more common in Africa than hitherto suspected. Thus, 20 out of 907 new patients attending the eye department of a large mission hospital in Ghana were diagnosed as having chloroquine retinopathy (23). In some of the cases reported from this same country, retinopathy was found to be associated with depigmented patches in the skin of the face and a greyish pigmentation of the mucosa of the hard palate (24). Ocular toxicity has also been identified as an industrial hazard. Eriksen (25) described acute corneal changes similar to those described after long-continued chloroquine therapy in workers exposed to chloroquine phosphate dust in the manufacture of chloroquine tablets.

Chloroquine retinopathy tends to be permanent after discontinuation of the drug, with visual acuity, visual field, and ophthalmoscopic examination remaining unchanged. However, a few patients in the early stages of retinopathy may show regression and occasionally a patient with a more advanced stage may show progression. In a recent review of the subject, Marks & Power (26) found that retinal changes associated with chloroquine occurred in 22 out of 222 patients undergoing long-term therapy for rheumatoid disease and that the changes were related to age, total dose, and duration of treatment. It is generally believed that a total dose of 200 g of chloroquine needs to be ingested over a period of two years or more before the appearance of ocular damage. Graniewski-Wijnands et al. (27) have suggested that in prolonged treatment with chloroquine, eye function should be monitored by regular measurement of the electro-oculogram. A decrease in the electro-oculogram of more than 20% of the value obtained before commencing treatment or a decrease to below 1.85 should be a reason for advising stopping the drug.

The mechanism of chloroquine-induced retinopathy is uncertain but it is widely presumed to be associated with the high affinity of chloroquine for melanin which is abundant in retinal tissue. Kuhn et

al. (28) found that flunitrazepam, which is similar to chloroquine and has high affinity for melanin in retinal cells, did not induce chloroquine-like retinal changes after long-term administration to cats and mice. Chloroquine under similar conditions induced the well-known changes. These investigators therefore concluded that the retinotoxic effect of chloroquine is not the result of its affinity for melanin-containing tissues and that the affinity of a drug for melanin-containing cells is not a sufficient reason for regarding it as potentially harmful to the eye.

Neuromuscular disorders

Mild neuromuscular disturbances, usually manifest as muscular weakness, are common during oral treatment of malaria with chloroquine. A few patients receiving chloroquine parenterally also complain of diplopia and difficulty in accommodation. These reactions are transient and disappear within a few minutes of administering the drug (11). A more florid polyneuropathy, sometimes associated with nystagmus (29), occasionally occurs during long-term treatment with chloroquine. The polyneuropathy generally resolves on stopping the drug. Chloroquine-induced neuromyopathy could be due to action of the drug on the nerve, muscle, or neuromuscular junction (30). Schmalbruch (31) induced myopathy in the soleus muscles of rats treated for 2–11 days with high doses of chloroquine. The muscle fibres showed autophagocytosis followed by segmental contracture and necrosis. A peculiar form of muscle pathology was described by Neville et al. (32) in a patient with systemic lupus erythematosus treated with chloroquine for 4 years. Nine years after cessation of chloroquine, muscle weakness developed. Muscle biopsy revealed inflammatory changes as well as distinctive cytosomes with curvilinear profiles similar to those reported in Batten's disease, a degenerative disorder of children which has a course different from that of systemic lupus erythematosus. The curvilinear profiles are thought to result from the effect of chloroquine.

Ototoxicity

Lesions of the inner ear leading to hearing disturbances are rare complications of chloroquine therapy (33). In a report from Nigeria, Mukherjee (34) described the case of a six-year old girl suffering from severe cochleovestibular dysfunction following a series of chloroquine phosphate injections. Prompt institution of therapy with steroids and vasodilators led to partial restoration of hearing. Experimentally, chronic administration of the so-called amphiphilic drugs (including chloroquine) has been shown to lead to an accumulation, in the inner ear, of lysosomes of different types containing phospholipids (35).

The ototoxicity of chloroquine may thus be due to its capacity to produce lipoidosis of the inner ear.

Other effects

Haematological abnormalities, especially leucopenia, can follow long-term administration of chloroquine. Intravascular haemolysis and renal insufficiency have been reported in patients with glucose-6-phosphate dehydrogenase deficiency.

Pigmentary changes in the skin occur occasionally during prolonged treatment with chloroquine. The skin of the face, neck, upper and lower limbs, buccal and palatal mucosa, and the nail beds of the fingers and toes are particularly susceptible. All these adverse reactions slowly disappear on stopping the drug.

Because chloroquine is used extensively in the treatment and prophylaxis of malaria at all stages of pregnancy, the question of possible teratogenicity has always been raised but so far there is no convincing evidence that chloroquine is teratogenic in man.

THE 8-AMINOQUINOLINES

The only 8-aminoquinoline antimalarial in common use in Africa is primaquine. In therapeutic doses, the side-effects associated with primaquine are mild and include anorexia, nausea and vomiting, epigastric discomfort, and abdominal cramps. With large doses toxic manifestations appear. Suppression of myeloid activity may lead to leukopenia and very rarely to agranulocytosis. Intravascular haemolysis leading to anaemia can occur in subjects with a genetically determined deficiency in the enzyme glucose-6-phosphate dehydrogenase. Cyanosis due to methaemoglobinaemia occurs frequently. It is most severe in subjects with congenital deficiency of the enzyme nicotinamide adenine dinucleotide methaemoglobin reductase, although all persons are normally susceptible. The toxicity of primaquine is increased by mepacrine, and so the two drugs are not given together.

QUININE

A characteristic collection of symptoms may occur in some persons during administration of quinine. This syndrome, which is commonly referred to as cinchonism and is due to idiosyncrasy to the drug in the affected persons, consists of giddiness, ringing in the ears, headache, nausea, and blurring of vision. These symptoms disappear on stopping the drug. Toxic doses of quinine produce more severe adverse reactions including severe gastrointestinal upset,

stimulation of the central nervous system followed by depression, renal damage, cardiac arrhythmias, and hypoprothrombinaemia and leukopenia. In pregnant women, overdosage may lead to abortion. Hypersensitivity reactions occur in some individuals and are manifest as pruritus, rashes, fever, and asthma. Intravenous injection of quinine can lead to a drastic fall in blood pressure and sudden death. This route is therefore best avoided unless in an emergency, when the drug can be given well diluted in a drip.

DIHYDROFOLATE REDUCTASE INHIBITORS

The main representatives of this class of antimalarials are proguanil and pyrimethamine. The only current use of proguanil is in the prophylaxis of malaria for which it is taken at a dose of 100 mg daily. It is well tolerated at the usual prophylactic dose. It also has a wide margin of safety between therapeutic and toxic doses.

At the recommended prophylactic dosage of 25 mg weekly, pyrimethamine is very well tolerated. At higher doses, for example prolonged administration of 25 mg daily for the treatment of toxoplasmosis, megaloblastic anaemia due to folic acid deficiency may develop. The risk of this complication may be reduced by the simultaneous administration of folinic acid, which corrects folic acid deficiency in the patient without abolishing the antimalarial action of the drug. The anaemia is also quickly reversed on stopping pyrimethamine. Pyrimethamine has been used extensively in the past 25 years in the prophylaxis of malaria during pregnancy. There is as yet no convincing evidence that it is teratogenic in man. If this risk exists at all, it appears to be much lower than the risk of abortion or fetal death due to malaria in the unprotected mother.

PYRIMETHAMINE PLUS SULFADOXINE OR DAPSONE

Fansidar is a combination of sulfadoxine and pyrimethamine while Maloprim combines dapsone with pyrimethamine. The adverse reactions to these drugs are largely those due to the sulfonamide or sulfone, respectively. The commonest unwanted effects of the sulfonamides are nausea, vomiting, abdominal discomfort, headache, and dizziness. Hypersensitivity reactions can occur in the form of drug fever and various types of rash. Very rarely, the hypersensitivity reactions may be more severe and present as polyarteritis nodosa or Stevens-Johnson syndrome. Blood dyscrasias, including aplastic anaemia and agranulocytosis, may occur. These severe reactions are less likely to occur at the usual therapeutic doses of Fansidar, but the danger is real when the drug is

used for prophylaxis. Thus Olsen et al. (36) recently reported severe reactions in three Europeans who used Fansidar for malaria prophylaxis during visits to certain malaria endemic countries. One patient had drug fever and photodermatitis, a second developed jaundice and toxic epidermal necrolysis, while the third developed agranulocytosis. The development of these toxic reactions with Fansidar is probably made more likely by the combination of the sulfonamide with another antifolate. Because of the risk of these severe untoward reactions it is probably unwise to use Fansidar for prophylaxis of malaria. Indiscriminate use of Fansidar for prophylaxis may also accelerate the development of resistant strains to this otherwise useful therapeutic agent.

Intravascular haemolysis may be precipitated by sulfonamides in individuals deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD). Cyanosis due to methaemoglobinaemia may also occur in subjects deficient in nicotinamide adenine dinucleotide methaemoglobin reductase. Since these two adverse reactions also occur with primaquine, caution must be exercised in combining the two drugs or even in using them sequentially.

The combination of pyrimethamine with dapsone, as in Maloprim, is effective in the prophylaxis of

falciparum malaria at an adult dose of one tablet (100 mg dapsone plus 12.5 mg pyrimethamine) per week. As with Fansidar, the side-effects of Maloprim are due predominantly to dapsone rather than to pyrimethamine. At the above doses, adverse reactions are uncommon. Cyanosis due to methaemoglobinaemia and intravascular haemolysis in G6PD-deficient individuals occur, as with the sulfonamides. Hypersensitivity reactions, particularly rashes, may occur; these may take the form of a transient erythematous or papular rash, fixed eruption, erythema multiforme, or toxic epidermal necrolysis. Haematological disorders, including bone marrow depression and megaloblastic anaemia due to folic acid deficiency, may also occur. This combination has been used extensively in various stages of pregnancy and there is no evidence that it is teratogenic in man.

CONCLUSION

In spite of the diverse side-effects and toxic reactions of the currently used antimalarials, these drugs are in general well tolerated when used correctly—in the right dose and by the right route—for the treatment of acute malaria or for its prophylaxis.

RÉSUMÉ

TOXICITÉ ET EFFETS SECONDAIRES DES ANTIPALUDÉENS EMPLOYÉS EN AFRIQUE; MISE AU POINT CRITIQUE

Malgré l'existence d'une chloroquino-résistance dans certaines zones d'Afrique, ce médicament reste l'antipaludéen le plus largement utilisé sur ce continent et l'un de ceux dont la toxicité et les effets secondaires ont été le plus étudiés. Le prurit constitue une réaction indésirable à la chloroquine, qui a une répercussion importante sur son utilisation. En dépit de l'accumulation de données ces dernières années sur l'incidence de cette réaction dans différents secteurs d'Afrique, on sait peu de chose sur son épidémiologie et, qui plus est, sur sa cause. La toxicité oculaire de la chloroquine est généralement associée à une utilisation prolongée du médicament, comme c'est le cas pour les troubles inflammatoires chroniques. Toutefois, étant donné l'utilisation croissante de la chloroquine en Afrique aux fins de la prophylaxie antipaludéenne, parfois à des doses atteignant 600 mg deux fois par semaine, le risque de voir augmenter l'incidence de cette réaction toxique est devenu bien réel et les médecins qui en prescrivent à titre prophylactique doivent avoir ce point présent à l'esprit.

Un autre antipaludéen susceptible d'être utilisé en Afrique à des doses croissantes est le Fansidar. Le risque d'une réaction indésirable sévère est probablement assez faible si on réserve ce produit au traitement des crises aiguës. En revanche, s'il y a utilisation au long cours à titre prophylactique, il faut compter avec les risques habituellement associés à l'utilisation des sulfamides à action prolongée.

Chez certains individus, les anomalies génétiques jouent également un rôle dans la fréquence et la gravité des réactions indésirables provoquées par certains médicaments. Par exemple, chez des malades présentant une carence en glucose-6-phosphate-déshydrogénase érythrocytaire, une hémolyse intravasculaire peut se produire après la prise de primaquine ou de quinine. Dans l'ensemble, la plupart des réactions indésirables courantes sont bénignes et influent peu ou pas du tout sur l'acceptabilité et l'utilisation de ces médicaments, si l'on excepte le prurit provoqué par la chloroquine. Il importe d'ailleurs d'étudier sans délai l'épidémiologie et la pathophysiologie précises de cette réaction.

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